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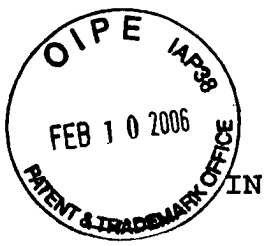


IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box AF

In re Application of)
)
Douglas H. ROBINSON)
)
Serial No. **08/719,367**) Examiner: J. Williams
)
Filed: September 25, 1996) Group Art Unit: 1643
)
For: METHODS FOR THE ISOLATION)
OF BACTERIA CONTAINING)
EUKARYOTIC GENES (AMENDED))

REQUEST FOR AMENDMENT AFTER FINAL REJECTION

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In response to the Office Action dated July 8, 1998, the Applicant respectfully requests reconsideration of the new rejections and the entry of the following Amendments. For the reasons set forth in the Remarks below, it is submitted that the Amendments address and overcome the new rejections, and place the claims in condition for allowance.

In the Claims:

Please amend as follows:

Claim 20, line 1, change "claim 1" to --claim 28--.

Cancel claims 33 - 38.

Rewrite claim 28 as follows:

--28. (Amended) A method for isolating a bacterium [that contains a eukaryotic and/or viral gene], comprising:

(a) preparing a culture of [cells selected from the group consisting of] retrovirally transformed human capillary microvascular endothelial cells (ATCC CRL 11655), [SV40-transformed human colon cells (ATCC CRL 1807), retrovirally-transformed porcine cerebral microvascular endothelial cells, L929 cells (ATCC CCL 1) and murine lymphoma cells (ATCC TIB52)] <u>in an aseptic, eukaryotic cell culture medium</u>,

(b) subjecting the culture of step (a) to an anaerobic culturing phase <u>under aseptic conditions</u> wherein the culture is subjected to anaerobic culturing conditions corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time of between about 18 and 24 hours, <u>followed by</u>

(c) exposing the culture <u>under aseptic conditions</u> to oxygen conditions corresponding to an atmosphere containing greater than 2 v/v % oxygen,

(d) re-subjecting the culture to <u>an</u> anaerobic culturing <u>phase under aseptic</u> conditions <u>wherein the culture is subjected to anaerobic culturing conditions</u> corresponding to an atmosphere of 0-2 v/v % oxygen, for a period of time of between about 18 and 24 hours, [and]

(e) subjecting the culture of step (d) to an aerobic culturing phase under aseptic culturing conditions and corresponding to an atmosphere containing greater than 2 v/v % oxygen in a bacterial culturing medium, and

[(e)](f) isolating from the culture of step (e) a bacterium [that contains a eukaryotic and/or viral gene].--

Remarks

Favorable reconsideration is respectfully requested in view of the preceding amendments and the following remarks. Claims 28-32 remain in the application and claims 33-38 have been canceled. Base claim 28 has been amended, and the amendments are discussed in detail below in connection with the rejections. No prohibited "new matter" has been added because all of the amendments find support in the specification.

Introduction

The applicant is grateful for the withdrawal of the previously pending rejections. The provisional double-patenting rejection has been withdrawn in view of the abandonment of the prior application, the Section 101 (lack of "credible utility") rejection has been withdrawn, the Section 112 lack-of-enablement rejections have been withdrawn, as has the Section 103 "obviousness" rejection.

In response to the newly presented Section 112 rejection, base claim 28 has been amended, without prejudice, to address and overcome the rejection. Claims 20-23 have been amended to correct their dependency. It is believed that all claims now are in condition for allowance.

The Section 112, 1st Paragraph, Rejections

The basis for the rejection in Paragraph 7 of the Office Action concerns the status of the deposit of the ATCC CRL 11655 cell line. This cell line was the "starting material" for many of the experiments reported in the application. Per the present amendments to the claims, this cell line now is the only starting material recited in the claims.

The ATCC receipt showing that the ATCC CRL 11655 cell line was deposited under the Budapest Treaty conditions accompanies this Amendment. This Amendment constitutes a statement by the Applicant's representative that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository.

The Applicant previously pointed out that the cited Blood article teaches the production of retrovirally-transformed cells that can be used as starting materials for the presently claimed inventive process. The Office Action incorrectly characterized the Applicant's argument as urging that the Blood article "provides a method for producing such bacteria." The Blood article does not teach any method for producing the end product of the claimed process; that is the novel teaching of the present application. It is hoped that this discussion clears-up any confusion regarding the teachings of the Blood article.

The rejection of Paragraph 8 of the Office Action concerns the scope of the claims. Base claim 28 has now been amended, without prejudice to seeking broader claims via the filing of one or more subsequent applications, to overcome this rejection. The Applicant firmly believes that the broader claims should be patentable, and thus does not intend these amendments to represent any acquiescence in the correctness of the rejection but, rather, a way to expedite prosecution to attain allowance of at least some claims.

First, the base claim has been amended to recite the ATCC CRL 11665 cell line as the sole starting material.

Second, the claim has been amended, in response to the Examiner's comments, to positively recite that cell

culturing is carried out in an aseptic, eukaryotic cell culture medium under aseptic conditions. Thus, the claims now positively exclude any process where the isolated bacteria originated merely as contaminants. It was not the Applicant's intention to claim contaminants.

Third, in response to the Examiner's criticisms, claim language stating that the isolated bacterium "contains a eukaryotic and/or viral gene" has been deleted from the claims. While it is recognized that commercial value of the present invention may lie in the production of bacteria that produce proteins encoded by, especially, eukaryotic genes, and the data in the present application shows the production of e.g. HSA, the Examiner's criticism of the language has been met by deleting it.

Fourth, base claim 28 has been amended to further specify the use (as used in the MA study) of an aerobic culturing step (now step (e)), also under aseptic conditions, from which the bacterium of interest is isolated. This addition brings claim 28 even closer to the exact process followed by MA.

Fifth, it is submitted that the amendments to the base claim -- specifically reciting a deposited starting cell line, the use of a eukaryotic cell culture medium, and the use of aseptic materials and conditions -- overcome the

criticism that the claims are not commensurate in scope with the MA Final Report. These are the same conditions and materials used by MA to verify the operability of the inventive method.

Finally, additional evidence that the present base claim is not overly broad is found in the accompanying one-page table that summarizes the data presented in the present application and in the MA Final Report. The isolation of bacteria according to the present invention is not a haphazard or "unpredictable" event. Bacteria were isolated in all of the experiments where ATCC CRL 11655 cells were used as starting materials in a process that included alternating anaerobic/aerobic culturing phases as recited in the present claims. In the various experiments, bacteria of the genera Bacillus, Staphylococcus and Micrococcus were isolated. Thus, in view of the fact that bacteria have consistently been isolated, but that the specific genus has varied, the scope of the present claims are amply supported.

The Section 112, Second Paragraph, Rejection

This rejection has been overcome by correcting the dependency of the claims.

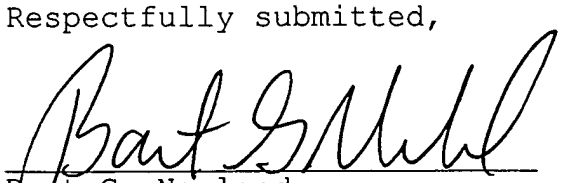
The Section 102 (Product-by-Process) Rejection

This rejection has been overcome by canceling claims 37 and 38.

Conclusions

In view of the preceding Amendments and Remarks, it is respectfully submitted that all of the Examiner's concerns have been overcome via amendments to the claims. All claims are believed to be in condition for allowance, and early notification of the same would be appreciated.

Respectfully submitted,

By 

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	
Douglas H. ROBINSON	**Box Issue Fee**
Serial No. **08/719,367**	**Batch: V87**
Filed: September 25, 1996	EXAMINER: M. ZEMAN GROUP: 1643
For: METHODS FOR THE ISOLATION OF BACTERIA CONTAINING EUKARYOTIC GENES (AMENDED)	

STATEMENT OF COMPLIANCE WITH REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

In response to the Requirement for the Deposit of Biological Material that accompanied the Notice of Allowance, Applicant herewith submits a copy of the ATCC receipt showing that the cultures designated as ATCC 55588, 55589, 55590, 55591 and 55592 were deposited under Budapest Treaty. This submission constitutes a statement by the Applicant's representative that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty and that all restrictions

upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application.

Respectfully submitted,

By _____

Bart G. Newland
Attorney for Applicant
Registration No. 31,282

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American Type Culture Collection

12301 Parklawn Drive • Rockville, MD 20852 USA • Telephone: (301)231-5520 Telex: 898-052 ATCCNORTH • FAX: 301-770-2587

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Douglas H. Robinson
Naval Medical Research Institute
Mail Code 514
Bethesda, MD 20889

Deposited on Behalf of: Secretary of the Navy and Douglas H. Robinson

Identification Reference by Depositor:	**ATCC Designation**
Cell, RT-HCMV, Clone II	CRL 11655

The deposit was accompanied by: __ a scientific description __ a proposed taxonomic description indicated above.

The deposit was received June 13, 1994 by this International Depository Authority and has been accepted.

AT YOUR REQUEST:

X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years after the date of deposit, and for a period of at least five years after the most recent request for a sample. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested June 14, 1994. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Bobbie A. Brandon Date: June 20, 1994

Bobbie A. Brandon, Head, ATCC Patent Depository

cc: Stephen G. Baxter, Ph.D.

Form BP4/9

EXPERIMENT NUMBER AND CELL TYPE*	EUKARYOTIC CELL CULTURE PHASE / OXYGEN CONDITION	BACTERIOLOGICAL CELL CULTURE PHASE / OXYGEN CONDITION	BACTERIOLOGICAL RESULT	ATCC DEPOSIT AND DESIGNATION OF BACTERIA
1 HUMAN / RETROVIRALLY TRANSFORMED (ATCC CRL 11655)	ALTERNATING AEROBIC / ANAEROBIC	AEROBIC	ONE GRAM-POSITIVE BACILLUS / *BACILLUS LICHENIFORMIS*	NONE
2 HUMAN / RETROVIRALLY TRANSFORMED (ATCC CRL 11655)	ALTERNATING AEROBIC / ANAEROBIC	AEROBIC	THREE GRAM-POSITIVE BACILLI / ALL *BACILLUS LICHENIFORMIS*	NONE
3 HUMAN / RETROVIRALLY TRANSFORMED (ATCC CRL 11655)	ANAEROBIC	AEROBIC	NO BACTERIA	N/A
4 HUMAN / RETROVIRALLY TRANSFORMED (ATCC CRL 11655)	ANAEROBIC	AEROBIC	NO BACTERIA	N/A
5 HUMAN / RETROVIRALLY TRANSFORMED (ATCC CRL 11655)	ALTERNATING AEROBIC / ANAEROBIC	AEROBIC	THREE GRAM-POSITIVE COCCI / ONE *MICROCOCCUS LUTEUS*/ ONE *STAPHYLOCOCCUS HEMOLYTICUS* / ONE UNTYPED	55588 55592
6 HUMAN / RETROVIRALLY TRANSFORMED (ATCC CRL 11655)	ALTERNATING AEROBIC / ANAEROBIC	AEROBIC	FIVE GRAM-POSITIVE COCCI / ONE *STAPHYLOCOCCUS AUREUS* / ONE *STAPHYLOCOCCUS CAPITIS* / ONE *STAPHYLOCOCCUS EPIDERMIDIS* / TWO UNTYPED	55589 55590 55591
7 PORCINE / RETROVIRALLY TRANSFORMED	ALTERNATING. AEROBIC / ANAEROBIC	AEROBIC	ONE GRAM-POSITIVE COCCUS / UNTYPED	NONE
8 MOUSE / RETROVIRALLY TRANSFORMED (ATCC CCL 1)	ALTERNATING AEROBIC / ANAEROBIC	AEROBIC	ONE GRAM-POSITIVE / UNTYPED	NONE
9 HUMAN / SV40-TRANSFORMED (ATCC CRL 1807)	ALTERNATING AEROBIC / ANAEROBIC	AEROBIC	TWO GRAM-POSITIVE COCCI / ONE GRAM-POSITIVE BACILLUS / UNTYPED	NONE
10 MOUSE / RETROVIRALLY TRANSFORMED (ATCC TIB52)	ALTERNATING. AEROBIC / ANAEROBIC	AEROBIC	ONE GRAM-POSITIVE BACILLUS / UNTYPED	
11 HUMAN / NO VIRAL TRANSFORMATION (ATCC HTB 38)	ALTERNATING AEROBIC / ANAEROBIC	AEROBIC	NO BACTERIA	N/A

* See patent application for detailed description of cell type(s).

- A total of 14 bacterial isolates were derived in the 11 experiments tabulated.
- Bacteria were isolated in 89% of experiments performed with an alternating aerobic/anaerobic condition during the eukaryotic cell culture phase. When human cells, designated as ATCC CRL 11655, were used as the starting material, bacteria were isolated in 100% of experiments performed with an alternating aerobic/ anaerobic condition during the eukaryotic cell culture phase. No bacteria were isolated in the experiments in which an anaerobic-only condition was used during the eukaryotic cell culture phase. Media-only controls were used in all experiments and were "negative" for bacterial growth in all.
- No bacteria were isolated in experiments using environmental/nutritional pressures other than that of an alternating aerobic/anaerobic condition. These experiments were numerous and are described in the patent application.

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12301 Parklawn Drive • Rockville, MD 20852 USA • Telephone: (301)231-5520 Telex: 898-055 ATCCNORTH • FAX: 301-770-2587

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3 AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Douglas H. Robinson
Naval Medical Research Institute
Mail Code 514
Bethesda, MD 20889

Deposited on Behalf of: Secretary of the Navy and Douglas H. Robinson

Identification Reference by Depositor:	ATCC Designation
Micrococcus, Isolate 1	55588
Staphylococcus, Isolate 2P	55589
Staphylococcus, Isolate 2W	55590
Staphylococcus, Isolate 5	55591
Staphylococcus, Isolate 1C	55592

The deposits were accompanied by: __ a scientific description __ a proposed taxonomic description indicated above.

The deposits were received June 13, 1994 by this International Depository Authority and have been accepted.

AT YOUR REQUEST:

X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years after the date of deposit, and for a period of at least five years after the most recent request for a sample. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested June 15, 1994. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Rockville, Md. 20852 USA

Signature of person having authority to represent ATCC:

Bobbie A. Brandon Date: June 20, 1994
Bobbie A. Brandon, Head, ATCC Patent Depository
cc: Stephen G. Baxter, Ph.D.